Remarks/Arguments

Applicants wish to thank the Examiner for withdrawing the previous 35 USC §103 rejection under the combination of Ghirri (US 6352974) and Bay (US20020065255), and the previous double patenting rejection over certain claims of copending Application No. US 11/577127.

Double Patenting Rejection

The Office maintains the outstanding double patenting rejection of claim 1 over claims 28 and 29 of copending Application No. US 12/093,383 and claims 1, 9 and 10 (and new claims 24-29) over claims 13-15 of copending Application No. 12/132,642.

The Office alleges that claims 13-15 of copending Application No. 12/132,642 render obvious current claims 1, 9 and 10 (and new claims 24-29) because claims 13-15 of copending Application No. 12/132,642 are directed to bone related diseases and calcium disorders. They are as follows:

Claim 12. (Currently Amended): A method for enhancing the oral bioavailability of a pharmacologically active polypeptide agent, said method comprising administering to a patient in need of a pharmacologically active polypeptide agent, an effective amount of a pharmaceutical composition according to claim 1.

Claim 13. (Currently Amended): A method of treatment of bone related diseases and calcium disorders comprising administering to a patient in need of such treatment a therapeutically effective amount of a composition according to claim 1, wherein said pharmacologically active polypeptide agent is a bone active agent.

Claim 14. (Currently Amended): A The method according to claim 13, wherein said pharmacologically active polypeptide agent is a calcitonin.

Claim 15. (Currently Amended): A The method according to claim 14 wherein said the calcitonin is salmon calcitonin.

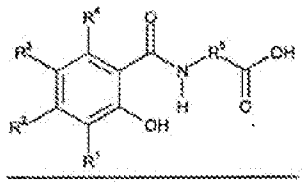
Claim 1 of copending Application No. 12/132,642, to which claims 12-15 refer, is as follows:

Claim 1. (Currently Amended): A solid pharmaceutical composition suitable for the oral delivery of a pharmacologically active agent comprising

a. a therapeutically-effective amount of a pharmacologically active polypeptide agent;

b. pharmaceutically acceptable inactive excipients, and

c. a delivery agent for said pharmacologically active agent of formula I



Formula I

wherein

R^1, R^2, R^3, and R^4 are independently hydrogen, -OH, $-NR^6R^7$, halogen, C_1-C_4alkyl, or C_1-C_4alkoxy;

R^5 is a substituted or unsubstituted C_2-C_{18}alkylene, substituted or unsubstituted C_2-C_{18}alkenylene, substituted or unsubstituted C_1-C_{12}alkyl(arylene), or substituted or unsubstituted aryl(C_1-C_{12}alkylene); and

R^6 and R^7 are independently hydrogen, oxygen, or C_1-C_4 alkyl; and hydrates, pharmaceutically acceptable salts and solvates thereof, wherein said delivery agent is in micronized form and has an average particle size of less than 10 microns.

Applicants note that claims 12-15 of copending Application No. 12/132,642 do not refer to calcitonin at all – and are instead directed methods of using a broad range of pharmaceutical compositions having a polypeptide agent.

Applicants note that claims 12-15 of copending Application No. 12/132,642 do not refer to 5-CNAC, SNAD or SNAC at all – and are instead directed methods of using a broad range of pharmaceutical compositions having a delivery agent as set forth in formula I.

Applicants note that the claims in this application are directed to the treatment of osteoarthritis, which is neither a bone related disease nor is it a calcium disorder as recited in claims 12-15 of copending Application No. 12/132,642. Indeed, as will be discussed below, osteoarthritis, which affects the cartilage of a joint, is a very different disorder than bone-related diseases (e.g., osteoporosis).

The Office also alleges that the dosage amounts recited in the instant claims, 0.2-1.2 mg calcitonin, are provided by Stern (US 5,912,014). This is not a proper double patenting analysis. For a double patenting rejection, the question is what claims 13-15 of copending Application No. 12/132,642 disclose – not what additional art discloses. In the instant situation – claims 13-15 of copending Application No. 12/132,642 do not recite any doses. The phrase "effective amount" may be interpreted as including the range found in the specification of copending Application No. 12/132,642 – namely 0.5 ug/kg – 10 ug/kg – which translates to a dose of 0.03 mg – 0.6 mg

for an average 60 kg human. This is a very large range compared to that found in Applicants' instant claims (0.2-1.2 mg). Thus, even if claims 13-15 of copending Application No. 12/132,642 were directed to the same disorder (or even a similar disorder) as the pending claims in this application (which they are not), the same polypeptide (which they are not) and the same carriers (which they are not), they would not render the pending claims in this application obvious.

The Office alleges that claims 28 and 29 of copending US 12/093,383 render obvious current claim 1 because claims 28 and 29 of copending US 12/093,383 are directed to the treatment of arthritic disease, e.g., osteoarthritis. They are as follows:

Claim 28. (Currently amended): ~~The use of the pharmaceutical composition of any one of claims 1 to 22 for the manufacture of a medicament for the treatment of~~ A method of treating an arthritic disease in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of claim 1.

Claim 29. (Currently amended): The ~~use~~ method of claim 28, where the disease is osteoarthritis.

Claim 1, to which claim 28 refers is as follows:

Claim 1. (Original): An oral pharmaceutical composition in the solid phase comprising:

iv. a poly(amino acid);

v. a delivery agent, and, optionally,

vi. a diluent;

wherein the composition has a disintegration time of no more than 10 minutes and a dissolution of >80% at 20 minutes.

Applicants note that claims 28 and 29 do not refer to calcitonin at all – and are instead directed methods of using a very broad range of pharmaceutical compositions having a ploy(amino) acid. This is not a disclosure of the use of calcitonin to treat osteoarthritis. Moreover, the Office alleges that the dosage amounts recited in the instant claims, 0.2-1.2 mg calcitonin, are provided by Stern. Again, this is not a proper double patenting analysis. For a double patenting rejection, the question is what claims 28 and 29 of copending US 12/093,383 disclose – not what additional art discloses. In the instant situation – claims 28 and 29 of copending US 12/093,383 do not recite any doses. The phrase "effective amount" may be interpreted as including the range found in the specification of copending Application No. US 12/093,383 – namely 0.5 ug/kg – 10 ug/kg – which translates to a dose of 0.03 mg – 0.6 mg for an average 60 kg human. This is a very large range compared to that found in Applicants' instant claims (0.2-1.2 mg). Thus, even if claims 28 and 29 of copending US 12/093,383

disclose did recite "calcitonin" (which they do not), they would not render the pending claims in this application obvious.

Moreover, as discussed in the previous response, and as discussed below, Applicants have shown unexpected and superior results for the inventive methods disclosed in the instant application. These unexpected and superior results are nowhere disclosed or suggested in either copending US 12/093,383 or copending Application No. 12/132,642. As a result, even if the Office had shown *prima facie* double patenting over certain claims of those copending applications, that *prima facie* case has been successfully rebutted.

Please withdraw the outstanding double patenting rejections.

Obviousness Rejections

The Office rejects pending claims 1, 6, 9, 10 and 24-29 under 35 USC §103 as being unpatentable over Stern in view of Kaplan (J. Am. Acad. Orthop. Surg. 1995, Vol 3(6)336-344) and further in view of Bay. The Office alleges that Stern teaches the use of an oral salmon calcitonin-containing pharmaceutical composition for treating osteoporosis and Paget's disease. The Office concedes that Stern does not teach the use of calcitonin to treat osteoarthritis. However, it is the position of the Office that Kaplan teaches that clinical manifestations of Paget's disease include osteoarthritis. The Office alleges that Stern teaches a desireable serum peak level of calcitonin (10-150 pg/mL, more preferably 10-50 pg/mL) and that this could allegedly be achieved using capsule dosage forms having 0.1-1 mg of calcitonin. For the following reasons, that rejection is respectfully traversed.

I. Obviousness Standards

Graham v. John Deere Co. of Kansas City, 383 U. S. 1, 17-18 (1966), establishes an objective analysis for applying §103 to a question of obviousness: "the scope and content of the prior art are . . . determined; differences between the prior art and the claims at issue are . . . ascertained; and the level of ordinary skill in the pertinent art resolved." The United States Patent and Trademark Office bears the burden of establishing a prima facie case of obviousness based on the results of the factual inquiries under *Graham*. The *prima facie* case generally requires three showings: 1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; 2) a reasonable expectation of success; and 3) that the prior art reference or combination of references teaches or suggests all the claim limitations. MPEP §2143.

The United States Patent and Trademark Office bears the burden of establishing a *prima facie* case of obviousness based on the results of the factual inquiries under *Graham*. The *prima facie* case requires three showings:

1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings;

2) a reasonable expectation of success; and

3) that the prior art reference or combination of references teaches or suggests all the claim limitations.

In the present application, the results of the factual inquiries under *Graham* do not support a *prima facie* case that the pending claims are obvious under 35 U.S.C. §103(a).

At the outset, Applicants' note that the Office has failed to answer Applicants' arguments in the previous response that relate to the difficulty in orally administering peptides and the fact that prior to Applicants' filing date no study had shown calcitonin to be effective in treating osteoarthritis in humans. (Previous Response, dated 7/27/2009 at pp. 8-10). As discussed previously, the first evidence that calcitonin could be used to treat osteoarthritis is provided by Applicants' disclosure. Calcitonin is widely understood to be an antiresorptive agent -- inhibiting bone resorption via its effect on bone osteoclasts. But prior to Applicants' disclosure there were widely conflicting reports about the effect, if any, that calcitonin had on cartilage and resulting osteoarthritis. Osteoporosis and osteoarthritis are two very different diseases requiring different treatments. Indeed, even today, Miacalcin® (an inhalable and injectable salmon calcitonin) is approved for Paget's diseases of bone, for the treatment of hypercalcemia and for the treatment of postmenopausal osteoporosis -- but it is decidedly NOT approved for treating osteoarthritis. Applicants' are the first to discover a method of using calcitonin to treat osteoarthritis.

As detailed in the prior response, before Applicants' priority date, one does not find disclosures that suggest that use of salmon calcitonin would have a reasonable expectation of success for the treatment of patients with osteoarthritis. This unpredictability regarding the use of calcitonin to treat osteoarthritis in any animal (including humans), coupled with the unpredictability inherent in attempting to orally deliver any protein, and the unpredictable bioavailability of orally administered calcitonin in a human (discussed in the previous response) firmly indicate that at the time of filing the instant application, there was no reasonable expectation of success in achieving Applicants' claimed methods. However, the Office has not answered those arguments, in contradiction to the requirement that the Office answer all

material traversed (MPEP 707.07(f)). It is not appropriate for the Office to simply ignore certain arguments – otherwise the principles of compact prosecution cannot be followed.

Instead of answering Applicants' previous arguments, the Office alleges that Stern teaches the use of oral calcitonin to treat Paget's disease. The Office then relies on Kaplan to establish that a complication of Paget's disease is osteoarthritis. The Office concludes that Stern must therefore teach the treatment of osteoarthritis using calcitonin. This is not only legally incorrect, but it is scientifically unsound. Paget's disease is a bone disease caused by accelerated bone remodeling, leading to weakened and deformed bone. (Kaplan p. 336). The manifestations are myriad, e.g., pain, spinal stenosis, back pain, tooth loosening, headache, increased heat, tenderness, cranial nerve function, associated arthritis, sarcoma, gout, asymmetrical limb development. (Kaplan p. 336). Osteoarthritis may be a complication of Paget's disease that occurs when, e.g., the bones under the cartilage of the joint change shape, the long bones bow or bend (placing stress on the joints), the spinal curvature changes, and/or the pelvis softens. Treating Paget's disease could alleviate complications that are associated with the bones affected by Paget's disease, but would have no effect on that complication if it were a separate disorder. This is because Paget's disease treatments do not address the complications independently. For example, people suffering from both Paget's disease and osteoarthritis who respond to their Paget's disease treatment can continue to experience arthritis-related pain. Why? Because existing treatments for Paget's disease do not treat osteoarthritis. (For a simple discussion of the difference between osteoarthritis and Paget's disease, see the NIAMS article "Paget's Disease of Bone and Osteoarthritis: Different Yet Related" [updated October 2005], available at http://www.niams.nih.gov/Health_Info/Bone/Pagets/pagets_osteoarthritis.asp and submitted herewith as part of an IDS).

Is the Office seriously contending that a skilled artisan would understand Stern and Kaplan to teach that calcitonin could be used to treat, e.g., a headache because headaches are associated with Paget's disease?[1] This cannot be, as no artisan would understand this to be true (see, e.g., the above referenced NIAMS article). As such, the conclusion that calcitonin could be used to treat osteoarthritis because it happens to be a complication of Paget's disease has no scientific support, and is not a proper use of inherency.[2] More importantly, the Office is required to construe Applicants' claims and consider what the prior art as a whole teaches. *W.L.*

[1] Applicants note the lack of approval of Miacalcin® for the treatment of headache.

[2] If the Office wishes to base an obviousness rejection on inherency, then the Office is required to show that when calcitonin is given to a Paget's patient, calcitonin treats osteoarthritis – not simply fortuitously alleviates osteoarthritis by alleviating Paget's disease.

Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (stating that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention). The present specification describes (and documents) on page 1 that, at the time of filing the instant application, no study had shown calcitonin to be effective in treating osteoarthritis in humans. The Office cannot ignore the teachings in the art that specifically relate to osteoarthritis and calcitonin and instead focus on the unrelated disorder, Paget's disease.

The Office also alleges that Stern teaches the dosages recited in Applicants' claims. Stern teaches that it is desireable to obtain a serum salmon calcitonin peak between 10-150 pg/mL, preferably between 10-50 pg/mL. Stern alleges that this serum salmon calcitonin peak could be obtained using 0.1-1 mg calcitonin per capsule. However, Stern dosages are found in Table 6, where dogs are orally dosed with either 5 or 10 mg calcitonin, and Table 7, where humans are orally dosed with 10.5 mg calcitonin in order to achieve therapeutic calcitonin levels. Stern is a single dose study to establish bioavailability, i.e., that the delivered calcitonin is taken up into the bloodstream. However, there is no evidence in Stern for any clinical efficacy in any disorder whatsoever since no biomarkers relevant to osteoporosis, Paget's Disease or osteoarthritis were measured, by contrast to the present application.[3] There is no evidence that Stern's delivery of calcitonin was effective for Paget's (which is at least mentioned in Stern), still less osteoarthritis. Stern teaches delivery - not effect. Thus, Stern does not provide a reasonable expectation of success for treatment of osteoarthritis, either alone or as a secondary symptom of Paget's, bearing in mind the lack of clear teaching in the prior art as to whether calcitonin has effect of osteoarthritis at all, let alone when delivered orally.

The Office's arguments relating to Stern dosage units (0.1-1 mg calcitonin per capsule) are irrelevant because the only dosage Stern tested in humans was 10.5 mg. In the previous obviousness-based rejection, the Office tried to use dosages allegedly taught by Ghirri. But, Ghirri did not use the carriers used by Applicants and therefore Ghirri simply could not provide any teaching or guidance as to how much calcitonin one might used in combination with, e.g., 5-CNAC. Now the Office chooses Stern for an obviousness rejection - but, like Ghirri, Stern does not use Applicants' delivery agent. Therefore, Stern also cannot teach or suggest an amount of calcitonin required to obtain good bioavailability with the form of carrier Applicants use. This is underscored by the fact that Stern had to use a very large amount of calcitonin, i.e., 10.5 mg calcitonin, to achieve what Stern believed to be acceptable bioavailability. Indeed, if the Office wishes to rely on Stern as teaching/suggesting a calcitonin dose for humans – then the fact that Applicants' can achieve therapeutic calcitonin levels with about ten-twenty times less than the

[3] Likely the Stern population was a population of healthy volunteers – which is typically used for a bioavailability study.

amount taught by Stern is quite surprising and for this reason alone the outstanding obviousness based rejection should be withdrawn.

But the Office misses the issue by focusing on calcitonin dosage (and, the puzzling discussion of Paget's disease) – the fact remains that before Applicants' disclosure, calcitonin was not known to be effective in relation to osteoarthritis or clinical markers of osteoarthritis. Moreover, it was well known that oral delivery of peptides was fraught with unpredictability. Given this, how can Applicants' methods, less so the oral delivery of calcitonin or the doses recited therein, be obvious or predictable?

Applicants wish to address the Office's assertions on page 11 of the instant Office Action that it is inappropriate to argue that Bay teaches away from Applicants' claimed dosages because Bay is designed to examine the effect of different additives on protein delivery. Applicants' respectfully submit that the Office has chosen Bay for an obviousness rejection.[4] The Office could have chosen a different reference with different dosages – the choice is the Office's, not Applicants'. Applicants are required to address what the Office has cited, i.e., what Bay teaches – and Bay teaches a very broad range of calcitonin dosages for humans (3.1 mg – 38 g)[5]. Applicants respectfully suggest that Bay likely selected calcitonin dosages that have some real world meaning in order to test the carriers therein. Accordingly, that Bay teaches a dose range for humans (3.1 mg – 38 g) in combination with, e.g., 5-CNAC, far outside of Applicants' dose range (0.4-1.2 mg) in combination with, e.g., 5-CNAC, is evidence of teaching away. Only the Bay reference can be fairly said to teach a dose range of calcitonin that one might used in combination with, e.g., 5-CNAC, and that dose range is clearly not what Applicants recite.

Stern teaches 10.5 mg calcitonin as a human dose. Bay teaches a human dose of 3.1 mg – 38 g. Where then is the calcitonin dose range of 0.4-1.2 mg found in Applicants' claims? The aforementioned feature of Applicants' methods cannot reasonably be said to be present in the asserted combination of references. The failure of an asserted combination to teach or suggest each and every feature of a claim remains fatal to an obviousness rejection under 35 U.S.C. § 103, despite any recent revision to the Manual of Patent Examining Procedure

[4] This argument made by the Office carries little weight given that the Office finds it perfectly acceptable to cite Stern as part of an obviousness rejection for a method of treating osteoarthritis; yet, Stern is quite clearly a study in delivery, not treatment, as no evidence of treatment of ANY disorder is disclosed in Stern.

[5] Conversion of the rat and monkey dosages in Bay to human dosages was obtained using the formula in Regan-Shaw et al. (2007) "Dose Translation from Animal to Human Studies Revisited" FASEB 22:659 [submitted herewith as part of an IDS]. This paper, incidentally, indicates that it is quite proper to translate animal doses (e.g., mouse) to human doses, in contrast to the Office's assertion on page 11.

(MPEP). Section 2143.03 of the MPEP requires the "consideration" of every claim feature in an obviousness determination. To render the instant independent claims unpatentable, however, the Office must do more than merely "consider" each and every feature for this claim. Instead, the asserted combination must also teach or suggest each and every claim feature. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (emphasis added) (to establish *prima facie* obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art). Indeed, as the Board of Patent Appeal and Interferences has recently confirmed that a proper obviousness determination requires that the Office make "a searching comparison of the claimed invention - *including all its limitations* - with the teaching of the prior art." *See In re Wada and Murphy*, Appeal 2007-3733, *citing In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). Further, the necessary presence of all claim features is axiomatic, since the Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including ascertaining the differences between the claimed invention and the prior art. *Graham*, 383 U.S. 1 (1966). Applicants submit that this is why Section 904 of the MPEP instructs examiners to conduct an art search that covers "the invention as *described and claimed*." (emphasis added). Lastly, Applicant respectfully directs attention to MPEP § 2143, the instructions of which buttress the conclusion that obviousness requires at least a suggestion of all of the features of a claim, since the Supreme Court in *KSR Int'l v. Teleflex Inc.* stated that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Finally, the Office dismisses Applicants' previous discussion of unexpected results on page 12 of the instant Office Action. That discussion is reproduced below.

> Assuming *arguendo*, that the Office has established a prima facie case of obviousness, he results provided for Applicants' methods rebuts any *prima facie* case of obviousness. (See MPEP 716.02(d) stating "To establish unexpected results over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range."). All claims currently recite treatment of osteoarthritis with dosages of either 0.4 – 1.2 mg, 0.8 - 1.2 mg, or about 1 mg of calcitonin. As evidenced by Applicants' results on page 26, these cited ranges provide unexpectedly beneficial results. In human clinical trials, the 1.0 mg dose shows benefit in reducing urinary CTX-1 at 3-month treatment (-19.7%) over the 0.4 mg dose (-15.12%), while the 2.5 mg dose did not show benefit (-17.5%) over the 1.0 mg dose. Moreover, page 26 discloses that women receiving 1.0 mg of calcitonin with 5-CNAC had the greatest reduction in 24-hour urinary CTX-1 compared to placebo. For CTX-II reduction, women who received 1.0 mg of calcitionin with 5-CNAC and were in the highest cartilage turnover at baseline had the greatest decrease in urinary CTX-II after 3-month treatment (compared to women in the lowest tertile). A similar trend was seen for the 0.4 mg dose. Further, aside from the clinical benefits seen with lower doses of calcitonin and 5-CNAC, e.g., 0.4 mg and 1 mg, a lower dose range is highly desireable because it decrease costs and the likelihood of adverse events.

The Office is correct that the components of the compositions used in Applicants' clinical trials are identical except for the amount of calcitonin. As the calcitonin compositions provided to the patients during clinical trials varied only in the amount of calcitonin, one may directly compare the efficacy of the different calcitonin dosages. Applicants are not required to also provide data showing superior results for different amounts of delivery agent. This is because different amounts of delivery agent are not recited as a claim feature. Applicants' method claims recite calcitonin dosages as a claim feature, and this dosage range shows surprising and unexpected results. Moreover, in Stern, clinicians used 10.5 mg of calcitonin (i.e., ten-twenty times the dosages recited in Applicants' method claims) in order to achieve therapeutic and acceptable blood levels of calcitonin in humans. Thus, Stern provides even additional evidence of the unexpected and superior properties associated with Applicants' inventive methods.

II. Summary

Based on the evidence as a whole, the combination of Stern, Kaplan and Bay does not support a finding of *prima facie* obvious. *See* MPEP § 2144.08; *In re Bell*, 991 F.2d 781,784 (Fed. Cir. 1993); *In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990)). The Office has not shown where all the elements of Applicants' pending claims may be found in the combination of the cited references, nor has the Office shown a reasonable expectation of success at achieving Applicants' claimed subject matter. In the present application, the results of the factual inquiries under Graham do not support that the pending claims are *prima facie* obvious under 35 U.S.C. §103(a). Moreover, as discussed in this and the previous Response (which is incorporated herein), the results provided in Applicants' specification and the results disclosed in the Stern reference show the surprising and unexpected properties of Applicants' inventive methods. Thus, any *prima facie* case of obviousness has been successfully rebutted. Accordingly, Applicants respectfully request withdrawal of the obviousness-based rejection of the pending claims.

CONCLUSION

In light of the above amendments, observations and remarks, Applicants respectfully submit that the presently claimed invention satisfies 35 U.S.C. §112, and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims in this application is earnestly solicited.

Applicants' undersigned attorney may be reached in our New Jersey office by telephone at (862) 778-9308. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
(862) 778-9308

Leslie Fischer
Attorney for Applicant
Reg. No. 58,393

Date: 11/10/09